УДК 618.19-006.04.44-033.2-07-085.277.3 Original research

PROGNOSTIC SIGNIFICANCE OF TUMOR-ASSOCIATED MACROPHAGES IN METASTATIC HER2-POSITIVE BREAST CANCER PATIENTS' SURVIVAL

O.I. Vynnychenko[1], Yu.V. Moskalenko[2], T.V. Derevianko[2], R.A. Moskalenko[2]

[1]Sumy Regional Clinical Oncology Center, Sumy, Ukraine;
[2] Sumy State University, Sumy, Ukraine.

Key words: *tumor-associated macrophages, survival, HER2, breast cancer, CD163+, CD68+.*

Bukovinian Medical Herald. 2024. V. 28, № 4 (112). P. 74-80.

DOI: *10.24061/2413-0737.28.4.112.2024.12*

E-mail: *vynnychenkool@ukr.net; yl.moskalenko@med.sumdu.edu.ua; tom4ukderevyanko@gmail.com; r.moskalenko@med.sumdu.edu.ua;*

Resume. *Recent studies indicate an essential role of the tumor microenvironment in the effectiveness of therapy and survival of patients with various types of cancers, including HER2-positive breast cancer. Tumor-associated macrophages are one of the most common immune cells of the tumor microenvironment, with both pro-tumorogenic and anti-tumorogenic properties.*
The aim *of our study was to clarify the prognostic role of M1 (CD68+) and M2 (CD163+) macrophages in patients with metastatic HER2-positive breast cancer.*
Material and methods. *We studied the tumor tissue of 78 patients with metastatic HER2-positive breast cancer. Tumor tissue samples underwent immunohistochemical examination with antibodies to CD68+ and CD163+ to determine the phenotype of M1 and M2 macrophages, respectively. Data on category T, category N and methods of drug therapy were obtained from primary medical records. Kaplan-Meier method, Cox regression analysis, and log-rank test were used for statistical analysis.*
Results. *The average duration of the follow-up period before registration of disease progression was 21.3±2.79 months. Median progression-free survival was 14.3 months and 13.2 months for patients with high and low CD68+ expression, respectively (Log-rank p=0.6168), and 14.9 months and 12.6 months for patients with low and high expression of CD163+, respectively (Log-rank p=0.0003). Follow-up of patients until death continued for an average of 35.0±2.98 months. Median overall survival was 24.1 months and 29.0 months for patients with high and low CD68+ expression, respectively (Log-rank p=0.5788), and 36.7 months and 22.0 months for patients with low and high expression of CD163+, respectively (Log-rank p=0.0001). Patients receiving a combination of trastuzumab with chemotherapy, without regional lymph node metastases, with low expression of CD163+, and those with hormone-positive HER2-positive breast cancer used hormone therapy have better overall survival.*
Conclusions. *High CD163+ expression is a predictor of poor progression-free survival and overall survival in patients with metastatic HER2-positive breast cancer. CD68+ expression did not show prognostic significance.*

ПРОГНОСТИЧНЕ ЗНАЧЕННЯ ПУХЛИНОАСОЦІЙОВАНИХ МАКРОФАГІВ У ВИЖИВАННІ ПАЦІЄНТІВ ІЗ МЕТАСТАТИЧНИМ HER2-ПОЗИТИВНИМ РАКОМ МОЛОЧНОЇ ЗАЛОЗИ

О. Винниченко, Ю. Москаленко, Т. Дерев'янко, Р. Москаленко

Ключові слова: *пухлиноасоційовані макрофаги, виживання, HER2, рак молочної залози, CD163+, CD68+.*

Буковинський медичний вісник. 2024. Т. 28, № 4 (112). С. 74-80.

Резюме. *Останні дослідження вказують на суттєву роль пухлинного мікрооточення в ефективності терапії та виживаності хворих на різні типи раку, у тому числі HER2-позитивного раку молочної залози. Пухлиноасоційовані макрофаги є одними з найпоширеніших імунних клітин пухлинного мікрооточення, які мають як протуморогенні, так і протипухлинні властивості.*
Мета дослідження *– з'ясувати прогностичну роль макрофагів М1 (CD68+) і М2 (CD163+) у пацієнтів із метастатичним HER2-позитивним раком молочної залози.*
Матеріал і методи. *Ми досліджували пухлинну тканину 78 пацієнтів з метастатичним HER2-позитивним раком молочної залози. Зразки*

пухлинної тканини піддавалися імуногістохімічному дослідженню з антитілами до CD68+ та CD163+ для визначення фенотипу M1 та M2 макрофагів відповідно. Дані про категорію T, категорію N та методи медикаментозної терапії отримані з первинної медичної документації. Для статистичного аналізу використовували метод Каплана-Мейєра, регресійний аналіз Кокса та логарифмічний ранговий критерій.

Результати. *Середня тривалість періоду спостереження до реєстрації прогресування захворювання становила (21,3±2,79) місяців. Медіана виживаності без прогресування становила 14,3 місяця та 13,2 місяця для пацієнтів із високою та низькою експресією CD68+ відповідно (Log-rank p=0,6168), 14,9 місяця та 12,6 місяця для пацієнтів із низькою та високою експресією CD163+ відповідно (Log-rank p=0,0003). Спостереження за пацієнтами до смерті тривало, у середньому (35,0±2,98) місяців. Медіана загальної виживаності становила 24,1 місяця та 29,0 місяця для пацієнтів із високою та низькою експресією CD68+ відповідно (Log-rank p=0,5788) та 36,7 місяця та 22,0 місяця для пацієнтів із низькою та високою експресією CD163+ відповідно (Log-rank p =0,0001). Пацієнти, які отримують комбінацію трастузумабу з хіміотерапією, без метастазів у регіонарні лімфатичні вузли, з низькою експресією CD163+, а також пацієнти з гормонально-позитивним HER2-позитивним раком молочної залози, які застосовували гормональну терапію, мають кращу загальну виживаність.*

Висновки. *Висока експресія CD163+ є предиктором поганої виживаності без прогресування та загальної виживаності у пацієнтів із метастатичним HER2-позитивним раком молочної залози. Експресія CD68+ не мала прогностичного значення.*

Introduction. Despite advancements in early diagnosis and treatment, breast cancer continues to be a significant issue globally. Among all subtypes, HER2-positive breast cancer, which expresses receptors for human epidermal growth factor 2, accounts for 14% of all cases. One of the most powerful factors determining patient survival is the tumor staging at the time of diagnosis. In patients with localized HER2-positive breast cancer, the 5-year survival rate is 94.0% and 84.2% for hormone-positive and hormone-negative types, respectively, but it drops to 45.8% and 39.7% in the case of metastatic stages [1]. The primary treatment for metastatic HER2-positive breast cancer is systemic drug therapy, which encompasses anti-HER2 monoclonal antibodies, chemotherapy, hormonal therapy, tyrosine kinase inhibitors, and antibody-drug conjugates [2].

Recent studies indicate the important role of the tumor microenvironment in the effectiveness of therapy and survival of patients with various types of cancers, including breast cancer [3]. The prognostic significance of tumor-infiltrating lymphocytes has been widely reported in the scientific literature [4, 5], while the role of tumor-associated macrophages in the response to drug therapy and progression of breast cancer is not definitively defined [6].

Among all immune cells of the tumor microenvironment, tumor-associated macrophages are most closely related to carcinogenesis and disease progression [7, 8]. These cells show significant heterogeneity and high plasticity. According to their properties, they are divided into two groups: antitumorogenic (M1-type macrophages), which are activated by the classical pathway, and pro-tumorogenic (M2-type macrophages), which are activated by an alternative pathway [9]. Macrophages of the M2 type are primarily associated with a worse prognosis [10, 11]. However, depending on the subtype of breast cancer, the prognostic effects may differ.

Although targeted therapy has significantly improved the survival of patients with HER2-positive breast cancer, this subtype is still considered aggressive, primarily due to treatment resistance that develops de novo or during anti-HER2 therapy [12]. The prognostic role of M1 and M2 macrophages has been evaluated in several studies involving patients with different stages of HER2-positive breast cancer. The results obtained were ambiguous. The authors reported both a negative effect of M2-type macrophages on patient survival [13] and an absence of correlation or a positive effect of M1-type macrophages [14], so we consider that the prognostic role of these cells has not been definitively determined. The ambiguity of the effects of tumor-associated macrophages may be related to the immunomodulatory effect of trastuzumab, which induces an antitumor immune response and changes the tumor microenvironment [15].

The aim of our study was to clarify the prognostic role of M1 (CD68+) and M2 (CD163+) macrophages in patients with metastatic HER2-positive breast cancer.

Materials and methods

Study design. We studied the tumor tissue of 78 patients treated at the Sumy Regional Clinical Oncology Center from 2014 to 2024. Patients with metastatic stages of HER2-positive breast cancer over the age of 18 were included in the study. All patients had archival tumor tissue samples and immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) results confirming HER2

receptor overexpression and HER2/neu gene amplification (if applicable). In addition, the inclusion criteria were monotherapy with trastuzumab or a combination of trastuzumab with chemotherapy (at least two cycles). The study did not include patients with localized breast cancer and those who, for some reason, did not receive trastuzumab therapy, had another malignant tumor, inflammatory, infectious, and autoimmune diseases 2 weeks before the start of specialized drug therapy. Data on category T, category N and methods of drug therapy were obtained from primary medical records. The follow-up period and assessment of response to therapy were described in our previous study [16]. Data on the death of patients were taken from the cancer registry of the Sumy Regional Clinical Oncology Center. The end date when patient survival was evaluated was July 1, 2024. The study was approved by the Local Ethics Committee of the Sumy Regional Clinical Oncology Center (protocol No. 2/3, dated January 15, 2024). All alive patients signed informed consent for voluntary participation in the study before the start of the study.

Immunohistochemistry. To carry out IHC examination of tumor tissue samples of HER2-positive breast cancer, we made serial sections with a thickness of 4 μm, which were applied to SuperFrost adhesive glass (Thermo Scientific, USA). Deparaffinized sections were treated with 0.1 M citrate buffer at 95–98 ◦C. The "In Vitro" system (Master-Diagnostica, Spain) was used for detection results. Antibodies to CD68+ (Master-Diagnostica, Spain) and CD163+ (Master-Diagnostica, Spain) were used to determine the phenotype of M1 and M2 macrophages, respectively. Passive and active control of the obtained results was carried out to control the quality of IHC. Six fields of view with a diameter of 1 mm and the highest density of the studied cells were analyzed. After this, we calculated the average value and divided all samples into high and low-expression groups. The cutoff values for M1 and M2 macrophages were 40 CD68+ cells and 25 CD163+ cells per field of view, respectively.

Statistical analysis. Statistical analysis was performed using Stata V.18.0 (StataCorp, Texas, USA; https://www.stata.com; 2024). The Kaplan-Meier method and the logarithmic test made it possible to visualize the survival curves and assess the reliability of the difference between the studied groups of patients. The Cox proportional hazards model predicted the impact of tumor-associated macrophages on progression-free survival and overall survival. The threshold of statistical significance was considered $p < 0.05$.

The results and discussion

Immunohistochemistry. During the IHC of breast cancer tissue, regarding the assessment of the presence of macrophages of the M1 phenotype among the tumor microenvironment, we found a wide range of these cells, from a small number to significant infiltration (Fig. 1 a, b). Macrophages were characterized by an intense positive cytoplasmic reaction against antibodies to CD68+ and were clearly detected in the tumor microenvironment. The primary location of M1 macrophages is the stroma of tumor tissue. Some macrophages were found in the tumor parenchyma among atypical glandular complexes and cells.

To assess the level of infiltration of the breast cancer tissue by M2-phenotype macrophages, we performed an IHC with antibodies against CD163+. The number of CD163-positive cells varied from single cells in the stroma to high infiltration of both the stroma and the parenchyma of the breast cancer tissue (Fig. 1 c, d). Macrophages of the M2 phenotype had an intensely stained cytoplasm and membrane, were mainly located in the stroma, and a certain number of CD163+ cells were present between the glandular complexes of the carcinoma.

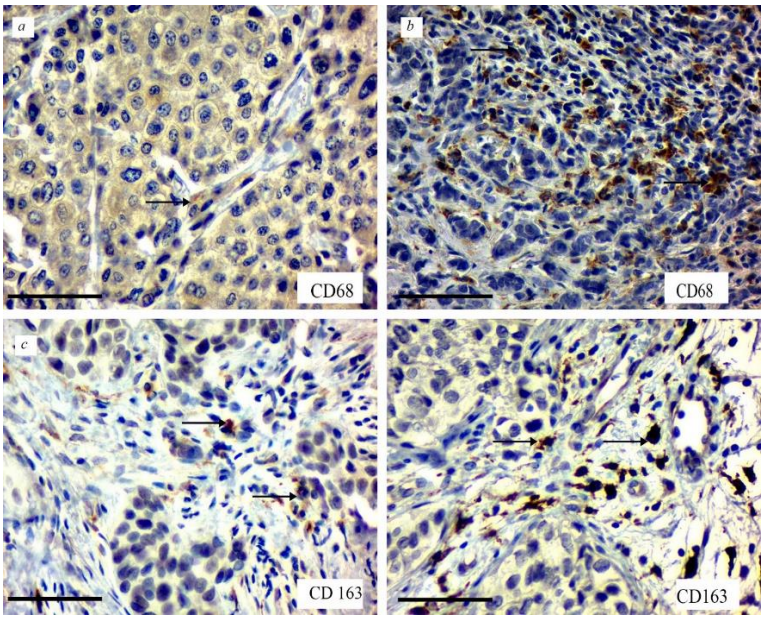

Fig. 1. Immunohistochemistry of the breast cancer tissue with antibodies against CD68+ (a, b) and CD163+ (c, d). Staining of nuclei with Mayer's hematoxylin. Magnification is indicated in the lower-left corner of each image as a marker corresponding to 200 μm

Characteristics of patients. Seventy-eight women with metastatic HER2-positive breast cancer participated in the study. Category T1-2 was registered in 39 (50.0%) patients. 38 (48.7%) patients had metastases in regional lymph nodes. Monotherapy with trastuzumab was performed for 27 (34.6%) patients and hormonal therapy - for 35 (44.9%) patients. 46 (59.0%) patients had hormone-positive breast cancer. High expression of M1 and M2 macrophages was determined in 31 (39.7%) and 40 (51.3%) patients, respectively (Table 1).

Impact of CD68+ expression on patient survival. The long-term follow-up period of patients began after the start of trastuzumab therapy. The average duration of the follow-up period before registration of disease progression was 21.3±2.79 months. During this period, 72/78 (92.3%) patients had disease progression, including 28/31 (93.3%) patients with high CD68+ expression and 44/47 (93.6%) patients with low CD68+ expression. Median progression-free survival was 14.3 months and 13.2 months for patients with high and low CD68+ expression, respectively (Log-rank p=0.6168; Fig. 2).

Follow-up of patients until death continued for an average of 35.0±2.98 months. Fatal outcomes of breast cancer were recorded in 69/78 (88.5%) patients, including 27/31 (87.1%) patients with high CD68+ expression and 42/47 (89.4%) patients with low CD68+ expression. Median overall survival was 24.1 months and 29.0 months for patients with high and low CD68+ expression, respectively (Log-rank p=0.5788; Fig. 3).

Table 1

Characteristics of the studied cohort of patients

Clinicopathological characteristics	Total number of patients, n=78
Category T, n (%)	
1–2	39 (50,0)
3–4	39 (50,0)
Category N, n (%)	
0	40 (51,3)
1–3	38 (48,7)
Hormonal status, n (%)	
Positive	46 (59,0)
Negative	32 (41,0)
Trastuzumab-containing regimen, n (%)	27 (34,6)
Trastuzumab monotherapy	51 (65,4)
Trastuzumab+chemotherapy	
Hormonal therapy, n (%)	
Present	35 (44,9)
Absent	43 (55,1)
Macrophages M1 (CD68+), n (%)	
>40 (high expression)	31 (39,7)
≤40 (low expression)	47 (60,3)
Macrophages M2 (CD163+), n (%)	38 (48,7)
<25 (high expression)	40 (51,3)
≥25 (low expression)	

Impact of CD163+ expression on patient survival. Disease progression was reported in 35/40 (87.5%) patients with low and 37/38 (97.4%) patients with high CD163+ expression. Median progression-free survival was 14.9 months and 12.6 months for patients with low and high CD163+ expression, respectively (Log-rank p=0.0003; Fig. 4).

Death occurred in 32/40 (80.0%) patients with low and 37/38 (97.4%) patients with high CD163+ expression. Median overall survival was 36.7 months and 22.0 months for patients with low and high expression of CD163+, respectively (Log-rank p=0.0001; Fig. 5).

Independent predictors of progression-free survival and overall survival. In Cox regression analysis, independent predictors of progression-free survival were

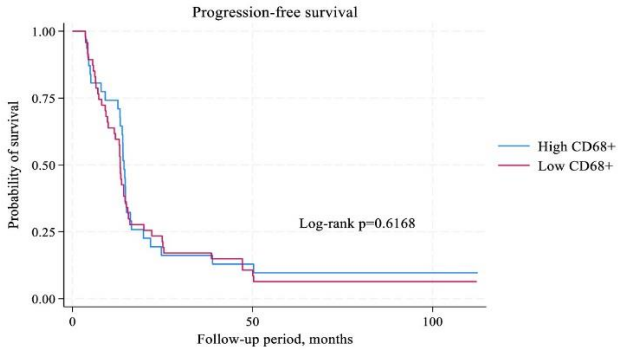

Fig. 2. Kaplan-Meier curves illustrating progression-free survival in patients with high and low CD68+ expression

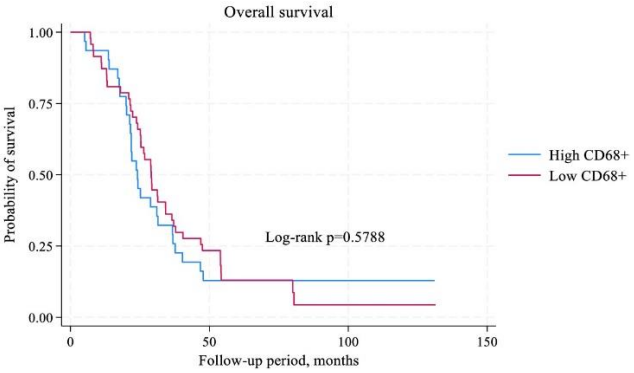

Fig. 3. Kaplan-Meier curves illustrating overall survival in patients with high and low CD68+ expression

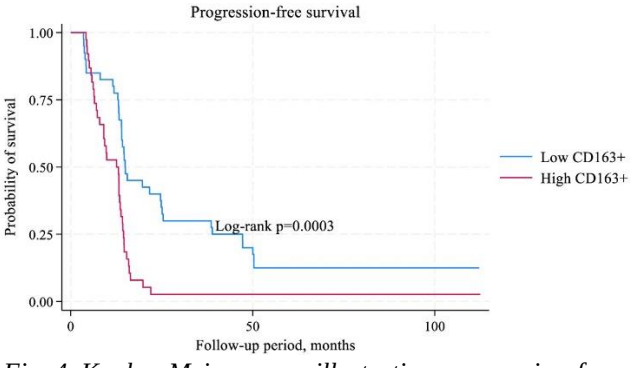

Fig. 4. Kaplan-Meier curves illustrating progression-free survival in patients with low and high CD163+ expression

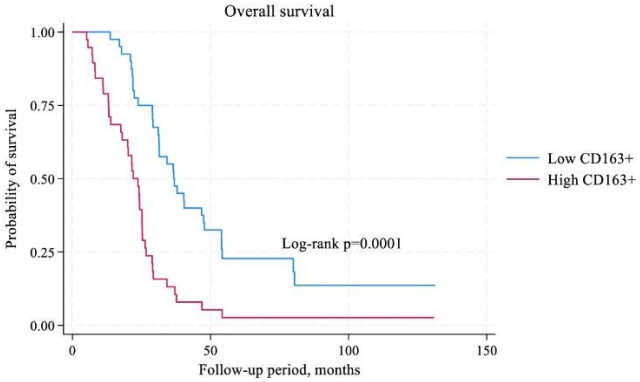

Fig. 5. Kaplan-Meier curves illustrating overall survival in patients with low and high CD163+ expression

hormone therapy, N category, and M2 macrophage expression. Patients with hormone-positive HER2-positive breast cancer receiving hormone therapy, without regional lymph node metastases, and those with low expression of CD163+ have better progression-free survival. Trastuzumab-based therapy regimen, hormone therapy, N category, and M2 macrophage expression were identified as independent predictors of overall survival. Patients receiving the combination of trastuzumab with chemotherapy, without regional lymph node metastases, with low CD163+ expression, and those with hormone-positive HER2-positive breast cancer using hormone therapy had better overall survival (Table 2).

We found that patients with low CD163+ expression had better progression-free and overall survival. CD68+ did not demonstrate an association with survival. This fact suggests that CD163+ is of great importance in the progression of HER2-positive breast cancer.

Immunological factors can potentially impact the effectiveness of antitumor therapy and patient survival, so this direction is actively researched [17]. All cells of the tumor microenvironment are closely connected. Pro-inflammatory and anti-inflammatory macrophages are involved in the pathogenesis of HER2-positive breast cancer. You et al. [18] found that overexpression of HER2 leads to increased secretion of chemokine ligand 2, which activates tumor-associated macrophages. Macrophage recruitment and active production of interleukin-8 and interleukin-1β, in turn, initiates carcinogenesis.

Table 2

Cox proportional hazards model determining predictors of progression-free survival and overall survival.

Clinicopathological characteristics	Progression-free survival			Overall survival		
	Hazard ratio	95% CI	p	Hazard ratio	95% ДІ	p
Trastuzumab-containing regimen (Trastuzumab monotherapy versus Trastuzumab+chemotherapy)	0,63	0,38–1,04	0,072	0,57	0,34–0,95	**0,032**
Hormonal therapy (present versus absent)	0,60	0,37–0,99	**0,046**	0,42	0,25–0,70	**0,001**
Category T (T1-2 versus T3-4)	1,31	0,78–2,21	0,294	0,92	0,54–1,57	0,771
Category N (N0 versus N1-3)	0,59	0,36–0,96	**0,037**	0,52	0,32–0,89	**0,016**
Expression of macrophages M1 (CD68+) (high versus low)	1,52	0,92–2,52	0,099	1,00	0,60–1,66	0,977
Expression of macrophages M2 (CD163+) (low versus high)	2,22	1,29–3,83	**0,004**	3,21	1,83–5,63	**0,001**

Stimulation of angiogenesis is another factor that leads to the progression of HER2-positive breast cancer. Kang et al. [19] described the role of the protein matrix metalloproteinase 11, which is contained in protumorogenic macrophages and leads to increased recruitment of monocytes and migration of tumor cells. In this study, HER2-positive tumors demonstrated more aggressive behavior than HER2-negative tumors. Tumor-associated macrophages are highly plastic, so an increase in the population of one phenotype may be due to increased recruitment or a shift from one phenotype to another (e.g., from M1 macrophages to M2 macrophages).

Our study demonstrated that the prognostic effect of CD163+ expression is independent of the use of trastuzumab. All patients enrolled in the study received trastuzumab therapy. However, patients with high CD163+ expression benefited less from treatment, resulting in poorer survival. Therefore, macrophages of the M2 type can reduce the effect of monoclonal antibodies against HER2. Some authors have studied the effect of macrophage polarization on the efficacy of anti-HER2 therapy and the survival of patients with HER2-positive breast cancer. They concluded that using drugs targeting the immunosuppressive microenvironment and anti-HER2 monoclonal antibodies may be a helpful approach to improve patient outcomes [20].

Targeted therapy aimed at polarization of macrophages may help overcome resistance to trastuzumab, which is particularly important in treating patients with metastatic disease [21]. An ongoing study investigates the efficacy and safety of a combination of HER2-targeted immunostimulatory antibody conjugate and anti-HER2 therapy in patients with metastatic HER2-positive breast cancer [22]. However, it should be considered that the

effectiveness of trastuzumab therapy can be influenced by tumor-associated macrophages and other cells, such as tumor-infiltrating lymphocytes [23]. This confirms the close interaction between the cells of the tumor microenvironment and their complex influence on the effectiveness of drug therapy.

In the current study, we found no prognostic significance of CD68+. This may be due to the heterogeneity of cells expressing these receptors [24]. However, CD163+ was an independent predictor of progression-free survival and overall survival. The obtained results coincide with the conclusions of other authors [25]. This allows the evaluation of CD163+ as a biomarker that can be successfully used in routine clinical practice to identify patients who will benefit from trastuzumab therapy. Moreover, our results are an additional argument for the need to develop targeted drugs to change the polarization of macrophages from M2 to M1. This approach will improve the prognosis for patients with HER2-positive breast cancer.

The current study has some limitations. We did not study the prognostic value of tumor-associated macrophages depending on the hormonal status of the tumor. Hormone therapy was a predictor of a better prognosis in patients with hormone-positive HER2-positive breast cancer. However, we did not evaluate the role of M1 and M2 macrophages in patients' survival depending on hormonal statuses.

Conclusions. High CD163+ expression is a predictor of poor progression-free survival and overall survival in patients with metastatic HER2-positive breast cancer. CD68+ expression did not show prognostic value. In addition, regional lymph node metastases, trastuzumab therapy, and hormonal therapy impact survival.

Prospects for further research. In the future, we plan to study the prognostic value of regulatory T-lymphocytes in patients with metastatic HER2-positive breast cancer.

References

1. SEER data, Female Breast Cancer Subtypes - Cancer Stat Facts Accessed November 12, 2024. https://seer.cancer.gov/statf acts/html/breas t- subty pes.html

2. Stanowicka-Grada M, Senkus E. Anti-HER2 Drugs for the Treatment of Advanced HER2 Positive Breast Cancer. Curr Treat Options Oncol. 2023 Nov;24(11):1633-50. DOI: 10.1007/s11864-023-01137-5.

3. Chao X, Liu L, Sun P, Yang X, Li M, Luo R, Huang Y, He J, Yun J. Immune parameters associated with survival in metaplastic breast cancer. Breast Cancer Res. 2020 Aug 18;22(1):92. DOI: 10.1186/s13058-020-01330-6.

4. Thomas N, Garaud S, Langouo M, Sofronii D, Boisson A, De Wind A, Duwel V, Craciun L, Larsimont D, Awada A, Willard-Gallo K. Tumor-Infiltrating Lymphocyte Scoring in Neoadjuvant-Treated Breast Cancer. Cancers (Basel). 2024 Aug 20;16(16):2895. DOI: 10.3390/cancers16162895.

5. El Bairi K, Haynes HR, Blackley E, Fineberg S, Shear J, Turner S, et al. The tale of TILs in breast cancer: A report from The International Immuno-Oncology Biomarker Working Group. NPJ Breast Cancer. 2021 Dec 1;7(1):150. DOI: 10.1038/s41523-021-00346-1.

6. Munir MT, Kay MK, Kang MH, Rahman MM, Al-Harrasi A, Choudhury M, Moustaid-Moussa N, Hussain F, Rahman SM. Tumor-Associated Macrophages as Multifaceted Regulators of Breast Tumor Growth. Int J Mol Sci. 2021 Jun 18;22(12):6526. DOI: 10.3390/ijms22126526.

7. Huang X, Cao J, Zu X. Tumor-associated macrophages: An important player in breast cancer progression. Thorac Cancer. 2022 Feb;13(3):269-276. doi: 10.1111/1759-7714.14268. Epub 2021 Dec 15. Erratum in: Thorac Cancer. 2022 Dec;13(23):3437. DOI: 10.1111/1759-7714.14709.

8. Larionova I, Tuguzbaeva G, Ponomaryova A, Stakheyeva M, Cherdyntseva N, Pavlov V, Choinzonov E, Kzhyshkowska J. Tumor-Associated Macrophages in Human Breast, Colorectal, Lung, Ovarian and Prostate Cancers. Front Oncol. 2020 Oct 22;10:566511. DOI: 10.3389/fonc.2020.566511.

9. Dieci MV, Miglietta F, Guarneri V. Immune Infiltrates in Breast Cancer: Recent Updates and Clinical Implications. Cells. 2021 Jan 23;10(2):223. DOI: 10.3390/cells10020223.

10. Allison E, Edirimanne S, Matthews J, Fuller SJ. Breast Cancer Survival Outcomes and Tumor-Associated Macrophage Markers: A Systematic Review and Meta-Analysis. Oncol Ther. 2023 Mar;11(1):27-48. DOI: 10.1007/s40487-022-00214-3.

11. Jeong H, Hwang I, Kang SH, Shin HC, Kwon SY. Tumor-Associated Macrophages as Potential Prognostic Biomarkers of Invasive Breast Cancer. J Breast Cancer. 2019 Mar;22(1):38-51. DOI: 10.4048/jbc.2019.22.e5.

12. Kreutzfeldt J, Rozeboom B, Dey N, De P. The trastuzumab era: current and upcoming targeted HER2+ breast cancer therapies. Am J Cancer Res. 2020 Apr 1;10(4):1045-67.

13. Tiainen S, Tumelius R, Rilla K, Hämäläinen K, Tammi M, Tammi R, Kosma VM, Oikari S, Auvinen P. High numbers of macrophages, especially M2-like (CD163-positive), correlate with hyaluronan accumulation and poor outcome in breast cancer. Histopathology. 2015 May;66(6):873-83. DOI: 10.1111/his.12607.

14. Honkanen TJ, Tikkanen A, Karihtala P, Mäkinen M, Väyrynen JP, Koivunen JP. Prognostic and predictive role of tumour-associated macrophages in HER2 positive breast cancer. Sci Rep. 2019 Jul 29;9(1):10961. DOI: 10.1038/s41598-019-47375-2.

15. Luque M, Sanz-Álvarez M, Morales-Gallego M, Madoz-Gúrpide J, Zazo S, Domínguez C, Cazorla A, Izarzugaza Y, Arranz JL, Cristóbal I, Rojo F. Tumor-Infiltrating Lymphocytes and Immune Response in HER2-Positive Breast Cancer. Cancers (Basel). 2022 Dec 8;14(24):6034. DOI: 10.3390/cancers14246034.

16. Vynnychenko OI, Moskalenko YV. Prognostic impact of body mass index on metastatic HER2-positive breast cancer survival. Ukrainian journal of radiology and oncology. 2024;32(3):363–76. DOI: https://doi.org/10.46879/ukroj.3.2024.363-376c

17. Onkar SS, Carleton NM, Lucas PC, Bruno TC, Lee AV, Vignali DAA, Oesterreich S. The Great Immune Escape: Understanding the Divergent Immune Response in Breast Cancer Subtypes. Cancer Discov. 2023 Jan 9;13(1):23-40. DOI: 10.1158/2159-8290.CD-22-0475.

18. You D, Kim H, Jeong Y, Yoon SY, Lo E, Kim S, Lee JE. Tumorigenicity of EGFR- and/or HER2-Positive Breast Cancers Is Mediated by Recruitment of Tumor-Associated Macrophages. Int J Mol Sci. 2023 Jan 11;24(2):1443. DOI: 10.3390/ijms24021443.

19. Kang SU, Cho SY, Jeong H, Han J, Chae HY, Yang H, Sung CO, Choi YL, Shin YK, Kwon MJ. Matrix metalloproteinase 11 (MMP11) in macrophages promotes the migration of HER2-positive breast cancer cells and monocyte recruitment through CCL2-CCR2 signaling. Lab Invest. 2022 Apr;102(4):376-90. DOI: 10.1038/s41374-021-00699-y.

20. Naji O, Ghouzlani A, Rafii S, Sadiqi RU, Kone AS, Harmak Z, Choukri K, Kandoussi S, Karkouri M, Badou A. Investigating

tumor immunogenicity in breast cancer: deciphering the tumor immune response to enhance therapeutic approaches. Front Immunol. 2024 Oct 23;15:1399754. DOI: 10.3389/fimmu.2024.1399754.

21. Vivekanandhan S, Knutson KL. Resistance to Trastuzumab. Cancers (Basel). 2022 Oct 19;14(20):5115. DOI: 10.3390/cancers14205115.

22. Li BT, Pegram MD, Lee K-W, Sharma M, Lee J, Spira AI, Hanna GJ, Kang Y-K, Rasco DW, Moore KN, et al. A Phase 1/2 Study of a First-in-Human Immune-Stimulating Antibody Conjugate (ISAC) BDC-1001 in Patients with Advanced HER2-Expressing Solid Tumors. J. Clin. Oncol. 2023;41:2358. DOI: 10.1200/JCO.2023.41.16_suppl.2538.

23. Jääskeläinen MM, Tiainen S, Siiskonen H, Ahtiainen M, Kuopio T, Rönkä A, Kettunen T, Hämäläinen K, Rilla K, Harvima I, Mannermaa A, Auvinen P. The prognostic and predictive role of tumor-infiltrating lymphocytes (FoxP3 + and CD8 +) and tumor-associated macrophages in early HER2 + breast cancer. Breast Cancer Res Treat. 2023 Sep;201(2):183-92. DOI: 10.1007/s10549-023-07017-8.

24. Song J, Xiao T, Li M, Jia Q. Tumor-Associated Macrophages: Potential Therapeutic Targets and Diagnostic Markers in Cancer. Pathol. Res. Pract. 2023;249:154739. DOI: 10.1016/j.prp.2023.154739.

25. Jamiyan T, Kuroda H, Yamaguchi R, Abe A, Hayashi M. CD68- and CD163-positive tumor-associated macrophages in triple negative cancer of the breast. Virchows Arch. 2020 Dec;477(6):767-75. DOI: 10.1007/s00428-020-02855-z.

Information about the authors

Vynnychenko O.I. – Ph.D, oncologist of Sumy Regional Clinical Oncology Center, Sumy, Ukraine. ORCID ID: https://orcid.org/0000-0001-5651-0323.

Moskalenko Y.V. – Ph.D, Associate Professor, Department of Oncology and Radiology, Sumy State University, Sumy, Ukraine. ORCID ID: https://orcid.org/0000-0002-5398-0298.

Derevianko T.V. – student of Medical Institute, Sumy State University, Sumy, Ukraine. ORCID ID: https://orcid.org/0009-0009-3518-0535.

Moskalenko R.A. – DM, Professor, Department of Pathology, Sumy State University, Sumy, Ukraine. +380979802731, ORCID ID: https://orcid.org/0000-0002-2342-0337.

Відомості про авторів

Винниченко О.І. - канд.мед.наук, хірург-онколог Сумського обласного клінічного онкологічного центру, м. Суми, Україна. ORCID ID: https://orcid.org/0000-0001-5651-0323.

Москаленко Ю.В. - канд.мед.наук, доцент, кафедра онкології та радіології Сумського державного університету, м.Суми, Україна. ORCID ID: https://orcid.org/0000-0002-5398-0298.

Дерев'янко Т.В. - студентка Медичного інституту (Сумський державний університет). ORCID ID: https://orcid.org/0009-0009-3518-0535.

Москаленко Р.А. – д-р мед. наук, професор, кафедра патологічної анатомії Сумського державного університету. ORCID ID: https://orcid.org/0000-0002-2342-0337.

Надійшла до редакції 12.11.24